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My patient chose to not use daily azithromycin to prevent exacerbation of COPD

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ABSTRACT A critical appraisal and clinical application of Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *New Eng J Med.* 2011;365:689-698. doi: 10.1056/NEJMoa1104623.

Keywords: *Chronic obstructive pulmonary disease, COPD, chronic obstructive pulmonary disease exacerbations, azithromycin*

Clinical Context

A 62-year-old gentleman presented to the emergency department with a two-day history of increased dyspnea and mildly productive cough. Symptoms started three days following the cessation of mild upper respiratory infection symptoms, including clear rhinorrhea, sore throat, and malaise. We diagnosed a COPD exacerbation through clinical presentation of increased dyspnea and sputum production, with supporting evidence through chest X-ray and arterial blood gases. Chest X-ray showed marked hyperexpansion, flattened diaphragm, and paucity of vascular structures. Arterial blood gases revealed acute-on-chronic respiratory acidosis. Additionally, a previous Pulmonary Function Test (PFT) showed post-bronchodilator FEV1, FVC & FEV1:FVC of 41%, 48% & 44% of predicted, respectively. The patient recalled similar symptoms in the past during his last admission for COPD exacerbation. He reported a 50-pack-year smoking history, but reports quitting one year ago. He denied any family history of pulmonary diseases. The patient was treated with supplemental oxygen, inhaled short-acting beta adrenergic agonists (Albuterol), inhaled short-acting anticholinergic agents (Ipratropium bromide), and intravenous glucocorticoids. The patient wondered if there were any other therapy regimen he could use to reduce the frequency of COPD-related exacerbations and improve quality of life, but was also concerned about additional side effects and compliance of taking additional daily medications. A medical record review of the patient revealed that on previous admissions for COPD exacerbations, he was treated with the same regimen as this admission, with the exception of antibiotics. Although it was not during every exacerbation, a macrolide or cephalosporin was added to the initial regimen on roughly half of the admissions. During the admission, the patient had a monitored average heart rate range of 70-80 bpm and measured QTc of 425 ms.

Clinical Question

Is there a benefit of azithromycin to reduce the frequency of acute exacerbations in patients with clinically diagnosed COPD?

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Research Article

Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *New Eng J Med.* 2011;365:689-698. doi: 10.1056/NEJMoa1104623

Related Literature

PubMED database was used to search for articles that contained keywords “azithromycin” OR “antibiotic” AND “chronic obstructive pulmonary disease” AND “chronic obstructive pulmonary disease exacerbations”. Majority of the articles assessed the efficacy of azithromycin to reduce the frequency of COPD-related exacerbations among specific subgroups of COPD patients, which our patient did not fit. Also, majority of the articles had a small patient population or other limitations. Other articles tested the efficacy of a wide range of antibiotics, but not specifically azithromycin. These articles were not helpful in answering the clinical question entirely, but were helpful in assessing the efficacy of azithromycin use in patients with COPD. One study followed several smaller studies that evaluated whether the macrolide-class of antibiotics decreased the risk of acute exacerbations of COPD (AECOPD) with conflicting results. It took a similar hypothesis of antibiotics to decrease the risk of AECOPD, but theorized antibiotic use as a supplement to the usual care of COPD patients and was the largest study population of its kind.[1] For this reason, Albert et al. was selected for critical appraisal. Two of the earlier studies showed no effect and very few exacerbations in either group. Of these two groups, one was a retrospective design[2] and the other was conducted for only three months.[3] The other studies from the database search did in fact establish that there is a decrease in AECOPD frequency with macrolide therapy. However, one study was not blinded[4], two did not include controls[5-6], and another only involved 35 patients.[7] Seemungal et al. in 2008 performed a randomized, 1-year trial of erythromycin that showed similar median time to first AECOPD as Albert et al. did with azithromycin. However, the Seemungal study found that the control group median time to first AECOPD was 85 days sooner. This may be true because nearly 40% of the participants in Seemungal study had three or more exacerbations in the previous year and were more current smokers[8], unlike our patient.

Seemungal et al. did establish the beneficial use of macrolide therapy to reduce the frequency of AECOPD and set the groundwork for future studies. The study was limited, but propelled the discussion of macrolide therapy in different subgroups of COPD. The limitations of this study included patient use of recent systemic glucocorticoids, number of previous exacerbations, and the reporting of exacerbations. The use of systemic glucocorticoids is a common form of therapy to treat AECOPD.[9] The 2008 study limited inclusion to patients that had not received systemic glucocorticoids for recent exacerbations. This is a common form of treatment and our patient had already received this type of therapy during his admission. In addition, although the number of recent AECOPD were recorded in the Seemungal study, it was not a criteria of inclusion or exclusion.[8] This could have lead to confounding results as some patients may not have had recent exacerbations or were not at risk for increased exacerbations. Since our patient had a recent AECOPD two months prior to admission, he was a better candidate for the study design by Albert et al.

The article chosen for this critical appraisal was a randomized, double-blinded, prospective, parallel-group, placebo-controlled trial of 1,142 subjects at 17 different sites. This study was one of the largest patient populations of its kind and across the largest range of sites. This article analyzed the median time to first exacerbation & frequency of exacerbation per patient-year. This study also required a history of recent exacerbation, but no sooner than four weeks prior to enrollment. Additionally, this study utilized the St. George’s Respiratory Questionnaire, which quantified the quality of life of patient with chronic airflow limitations.[10] Monitoring and improving quality of life was especially important to our patient. Therefore, this study by Albert et al. was most relevant to our clinical question and context, as this study analyzed the largest population with the most specific criteria that met our patient’s situation.

Critical Appraisal

The article by Albert et al. was a prospective, parallel-group, double-blinded, placebo-controlled design trial[1], which falls under a level 1B level of evidence according to the Oxford Centre for Evidence-Based Medicine. Participants were recruited from March 2006 to June 2010 in 17 sites with 12 academic health centers in the United States. Patients were scheduled with a follow-up every three months for one year and additionally monitored during each subsequent clinic visit and determined whether an AECOPD had occurred. Patients had nasal swab performed at enrollment and at every three-month visit. The purpose of the study was to

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determine whether or not azithromycin decreased the frequency of AECOPD in patients who were at an increased risk of COPD-related exacerbations. This study followed the article from Martinez et al. that concluded macrolide antibiotics have additional beneficial effects that are independent of their antibacterial profile. These anti-inflammatory effects have particular importance in chronic inflammatory airway disorders, such as COPD. Martinez et al. assessed multiple previous studies that identified the anti-inflammatory and anti-secretory effects of macrolides. The study concluded that macrolides have the ability to increase phagocytosis of apoptotic neutrophils and decrease pro-inflammatory cytokine production, reactive oxygen species, and chemotaxis. Above all, these effects showed the ability of macrolides to reduce chronic airway inflammation and mucus production in chronic inflammatory airway diseases, such as COPD.[11]

The 1142 participants in the study were randomly assigned to one of two groups in a 1:1 ratio. The first group was to receive azithromycin (570), at a dose of 250 mg orally, and the other group was to receive an identical-appearing placebo (572). Both groups received the study therapy daily for 1 year, in addition to their usual treatment. The groups were otherwise treated equally. Patients were selected for this study if they had a clinical diagnosis of COPD (defined as having a post-bronchodilator FEV1 of <80% predicted value, post-bronchodilator ratio of FEV1 to FVC of <70%, and a smoking history of at least 10 years), were using continuous supplemental oxygen or had received systemic glucocorticoids within the last year, had an AECOPD requiring either an emergency room visit or hospitalized admission, but not within the last four weeks, and were at least 40 years of age. Patients were excluded if there was a previous history of asthma, resting heart rate greater than 100 bpm, prolonged QTc >450 msec, taking any medication that may prolong QTc or any hearing impairment documented by audiometric testing. The latter three exclusions were particularly important as they are directly related to the risks of azithromycin use. Our patient had satisfied all inclusion and exclusion criteria included in this study and we concluded that the therapeutic protocol would be feasible.

The main primary outcome of this study was the time to the first AECOPD. For this study, an AECOPD was defined as increased or new onset respiratory symptoms with at least two of the following: cough, dyspnea, chest tightness or wheezing for a duration of at least three days. The secondary outcome was adherence to taking the study drug as directed, quality of life, and nasopharyngeal colonization with select respiratory pathogens. Swabs were collected at time of enrollment and every three months to assess for pathogen associated with macrolide resistance. Pathogens included Staphylococcus aureus, Streptococcus pneumoniae, haemophilus species, and moraxella species. Adverse events associated with azithromycin therapy included audiogram-confirmed hearing decrement and non-fatal events, such as pneumonia, GI tract and cardiovascular events.

The analysis was performed using an intention-to-treat analysis, which showed the risk of AECOPD reduced in the azithromycin group. This study had 495 subjects in the intervention group that completed the study (25 lost to follow-up) and 502 subjects in the placebo group that completed the study (22 lost to follow-up). With a low lost to follow-up rate (4.4% and 3.8%), the data is complete with minimal bias.[12] Median time to the first AECOPD was 266 days (95% CI, 227 to 313) in the azithromycin group and 174 days (95% CI, 143 to 215) in placebo group (P<0.001). Additionally, rates of AECOPD per patient-year were 1.48 and 1.83, respectively (P=0.01, 95% CI, 0.72 to 0.95). The number needed to treat to prevent one acute exacerbation of COPD was 2.86. No significant differences were observed in the frequency of serious adverse events or of adverse events leading to discontinuation of the study drug. Secondary outcomes measured other tangible changes of long-term azithromycin use, other than AECOPD. In the azithromycin group, mean adherence to medication was 67.3%, compared to 66.9% in the placebo group (P=0.84). Total St. George Respiratory Questionnaire scores recorded at 1 year were reduced by a mean (±SD) of 2.8±12.8 units in the azithromycin group, compared to a mean reduction of 0.6±11.4 units in the placebo group, indicating an improve quality of life in the azithromycin group.[10] Nasopharyngeal colonization showed resistance to macrolides in 81% of the azithromycin group and 41% of the placebo group.

One downside of the study were the effects of long-term azithromycin use. Audiogram-confirmed hearing decrement occurred in 142 subject receiving azithromycin (27%), as compared to 110 subjects receiving placebo (21%). Additionally, the increased resistance in the azithromycin group may put the patient at greater risk for infection with drug-resistant respiratory pathogens. It is important to note that patients were excluded from this study for baseline QTc prolongation or tachycardia, as these are addition parameters that may be exacerbated in chronic macrolide therapy. One area of concern is the duration and frequency of azithromycin administration. Albert et al. states that daily dosing was done to facilitate better adherence. However, it is possible that lower doses or less frequent administration may have produced similar results, with fewer risks and side effects of long-term macrolide therapy. Similarly, even though the azithromycin group had a reduced the risk of AECOPD, the proportion free from

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AECOPD was roughly parallel in the study group as compared to the control group after 120 days. Further study could look into the same use of daily azithromycin for 120 days, but with follow-up for an entire year, as there may be long-lasting effects on reducing AECOPD risk. Banerjee et al. had already demonstrated that there is no benefit of daily macrolide use for 3 months, but did not use 250 mg azithromycin and did not continue follow-up after drug discontinuation. Of concern is the possibility of participation bias, as it was unclear exactly how the subjects were recruited for this study. Also, there is a potential for publication bias, as authors of the study disclosed potential conflicts of interest due to receiving research grants, consulting fees, payment for service of advisory boards for pharmaceutical companies, and holding stock, among other conflicts of interest.

Clinical Application

Albert et al., in agreement with this critical appraisal, concluded that adding 250 mg of azithromycin daily for one year to the usual treatment of patients of COPD decreased the frequency of AECOPD and improved quality of life. This benefit was observed in patients that have had an AECOPD within the previous year and those who require supplemental oxygen or systemic glucocorticoids. Our patient fit the above-mentioned criteria for the Albert et al. study. He was a gentleman with clinically diagnosed COPD that had history of recent AECOPD and requiring supplemental oxygen. His genuine curiosity for improved quality of life and reduced of AECOPD sparked the discussion for the database search and appraisal. However, the patient was not willing to take more daily medication indefinitely and was concerned about adverse effects, so the patient was not started on the azithromycin therapy, even though the benefits were explained thoroughly to the patient. Therefore, internal validity of this study can be proved from the results of the study, but external validity cannot apply to this particular patient, as the patient specifically does not wish to take additional daily medication.

Learning points:

1. There is a benefit of daily azithromycin to reduce the frequency of AECOPD
2. The obvious benefit of one therapy does not supersede the additional risks or burdens on a patient.
3. Further studies are needed to explore if there is similar benefit of azithromycin use in reducing AECOPD, but in lower doses or less frequency.

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